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Trends in Glyburide Compared With Insulin Use for Gestational Diabetes Treatment in the United States, 2000–2011

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Abstract

Objective—To describe trends and identify factors associated with choice of pharmacotherapy for gestational diabetes (GDM) from 2000–2011 using a healthcare claims database.

Methods—This was a retrospective cohort study of a large nationwide population of commercially insured women with GDM and pharmacy claims for glyburide or insulin prior to delivery, 2000–2011. We excluded women younger than 15 years or older than 50 years, those

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with prior type 2 diabetes, or those who had multiple gestations. We estimated trends over time in the use of glyburide compared with insulin and prevalence ratios (PR) and 95% confidence intervals (CI) for the association between covariates of interest and treatment with glyburide compared with insulin.

Results—We identified 10,778 women with GDM treated with glyburide (n=5,873) or insulin (n=4,905). From 2000–2011, glyburide use increased from 7.4% to 64.5%, becoming the more common treatment in 2007. Women less likely to be treated with glyburide were those with metabolic syndrome (PR=0.71, 95%CI: 0.50– 0.99), hyperandrogenism (PR=0.77, 95%CI: 0.62–0.97), polycystic ovarian syndrome (PR=0.88, 95%CI: 0.78–0.99), hypothyroidism (PR=0.89, 95%CI: 0.83–0.96) or undergoing infertility treatment (PR=0.93, 95%CI: 0.86–1.02). The probability of receiving glyburide decreased by 5% for every 10-year increase in maternal age (PR=0.95, 95%CI: 0.91–0.99). Among women prescribed with glyburide, 7.8% switched or augmented to a different drug class compared with 1.1% of insulin initiators.

Conclusion—Glyburide has replaced insulin as the more common pharmacotherapy for GDM over the last decade among those privately insured. Given its rapid uptake and the potential implications of suboptimal glucose control on maternal and neonatal health, robust evaluation of glyburide's relative effectiveness is warranted to inform treatment decisions for women with gestational diabetes.

INTRODUCTION

The prevalence of gestational diabetes mellitus (GDM) in the United States more than doubled from 1.5% in 1989–1990 to 4.2% 2001–2004. Between 7–35% of diagnosed women will require pharmacological treatment during pregnancy (1). The only Food and Drug Administration approved medication for the treatment of GDM is insulin (2) although glyburide (an oral agent), is also used (3).

Glyburide is a second generation sulfonylurea, thought to be effective for the treatment of GDM (4). Glyburide is believed to be safe based on results from animal and *in-vitro* placental studies showing minimal transfer (5, 6), although recent studies in humans have shown fetal transfer (7). Its ease of use and low cost are advantages compared to insulin which is administered by injection and entails higher costs (8).

In 2000, Langer et al. conducted the first randomized controlled trial (RCT) comparing glyburide to insulin in 404 women with GDM (9). Since then, two more RCTs (10, 11), three observational studies (12–14) and two meta-analyses (15, 16) have compared the efficacy or effectiveness of the two drugs. It is unknown how evidence from these studies has affected choice of medication in routine practice and which factors influence the prescription of glyburide compared with insulin. There are no current estimates of the dissemination of glyburide use during pregnancy, in the US population.

Our objective was to characterize pharmacological treatment of women with GDM by describing trends in the use of glyburide compared with insulin over the last decade, and identifying predictors of initial choice of pharmacotherapy.

MATERIALS AND METHODS

We conducted a retrospective cohort study of women with gestational diabetes identified in Truven Health's MarketScan Commercial Claims and Encounters database from 2000–2011. This database is the largest collection of claims from patients with employer-sponsored health insurance in the United States (17). Data from individual patients are integrated from all providers of care over time, for as long as the patient is enrolled in the employer's health plan. Truven Health Analytics reviews all claims and enrollment data to ensure completeness, accuracy, and reliability.

The database has information from over 100 payers of private health insurance for employees and their dependents, covering more than 25 million lives annually. It contains details of enrollment, demographics (age, sex, geographic region), inpatient/outpatient services, and outpatient pharmacy data. These data include information about diagnoses (ICD-9-CM diagnosis codes) and procedures (CPT-4 and ICD-9-CM procedure codes), in the outpatient and inpatient settings reported on administrative claims. Data on prescription medications (National Drug Codes) filled through outpatient pharmacies are also reported using insurance claims. Each enrolled individual is assigned a unique, encrypted identification number making it possible to link records and obtain nearly comprehensive record of encounters with the health care system.

We identified women who had claims for delivery of a live born infant through the use of ICD-9 diagnosis, procedure and CPT-4 codes (see the Appendix online at http://links.lww.com/xxx). Because multiple claims can be generated during delivery care, we grouped those occurring consecutively and defined delivery date as the date of the earliest claim. Women were required to be continuously enrolled during the year prior to and at least three months after the delivery date (Figure 1A).

For each delivery, we identified women who had a claim with a diagnosis code for GDM (ICD-9-CM 648.8–648.83) in the year prior to delivery date. If two deliveries occurred within a 12-month period, GDM diagnosis codes for the second pregnancy were assessed in the period beginning 6 weeks after the delivery date of the first pregnancy. The six week period was used to avoid capturing GDM diagnosis codes which might occur postpartum from the first pregnancy (Figure 1B). We excluded women 1) with diagnosis codes for type 1 or 2 diabetes; 2) younger than 15 years or older than 50 years old; and 3) with diagnosis or procedure codes for pregnancy with multiple gestations. Our cohort was restricted to the first eligible GDM pregnancy for a given woman.

We identified women in our cohort with a pharmacy claim for insulin or glyburide using NDC codes. Women were classified as insulin or glyburide initiators based on the drug class of their first claim; the date on this claim was defined as initiation of pharmacotherapy (index date). We excluded those initiating pharmacological treatment after delivery or who had an index date occurring earlier than 150 days before delivery (suggestive of management for pre-pregnancy type 2 diabetes). We also identified treatment changes occurring after the index date but prior to delivery. Change in pharmacotherapy was defined as any claim occurring after the index date for a drug class different to that prescribed at

initiation. We also identified a group of women with GDM who were not treated pharmacologically within 150 days of delivery. We excluded from this analysis women whose index prescription was for thiazolidindiones (n=181) or acarbose (n=27).

We identified characteristics that might influence the choice of initial therapy (insulin or glyburide) for GDM. All characteristics were defined through the use of ICD-9-CM diagnosis or CPT-4 codes, and assessed before the index date. Comorbidities of interest were: infertility diagnosis (ICD-9-CM V26.8, V26.81 CPT-4 89252, 89268, 89281, 58310, 58311, 58321–23, 58970–76, 89250–57, 89268, 89272, 89280–81, 89290–91, 89352–54) or treatment (at least 1 claim for clomiphene, urofollitropin, follitropin, menotropin, ganirelix, cetrorelix); obesity (ICD-9-CM 278.0X, 649.1X, V77.8, V85.3x, V85.4); hypothyroidism (ICD-9-CM 244.X); hyperandrogenism (defined as an ICD-9-CM code for alopecia [704.0X], hirsutism [704.1] or acne [706.0, 706.1]); metabolic syndrome (ICD-9-CM 277.7); and polycystic ovarian syndrome (ICD-9-CM 256.4). Because metformin is used off label for infertility or to reduce risk of miscarriage we identified use of metformin early in pregnancy (>150 days prior to delivery) and used this as a covariate in the analyses.

Trends in the use of glyburide compared with insulin between years 2000–2010 were estimated by calculating the proportion of women who initiated glyburide, using as denominator the total number of women treated with medication in a given year. Multivariable log-linear regression was used to estimate average annual percent change and 95% confidence intervals (CI) in the use of glyburide for the overall period and within intervals of interest (18). Binomial regression was used to adjust for covariates of interest using fractional polynomials to flexibly model the association between age and choice of initial therapy (19). We estimated prevalence ratios (PR) and 95% CI for the association between baseline characteristics (age, region, comorbidities, calendar time) and treatment with glyburide compared with insulin. To estimate the association between drug class at initiation and risk of change we calculated Risk Ratios (RR) and 95%CI.

All analyses were conducted using SAS v 9.3 (SAS Institute, Cary, NC). This study using existing, de-identified data was determined to be exempt from further review by the Public Health –Nursing Institutional Review Board, Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

RESULTS

Among women with a delivery code and who met our enrollment criteria (N=1,108,383), 122,064 had an eligible pregnancy complicated by GDM. Of these women, 10,778 (8.1%) had a pharmacy claim for insulin (n=4,905) or glyburide (n=5,873) during the 150 days prior to delivery. Among women treated pharmacologically the use of glyburide increased monotonically from 7.4% in 2001 to 64.5% in 2011 becoming the more common treatment since 2007 (Table 1). Comparing glyburide with insulin, the adjusted annual percent change was higher between 2000–2007 (34.0% 95%CI 20.4,49.1) and reached a plateau after 2008 with an annual increase of 3.7% (95%CI 0.8,6.7). The increase was observed across all age groups (Figure 2).

Among women treated with glyburide or insulin, the mean age at baseline was 33 years (SD 4.9) compared to 32 (SD 5.2) years in those not treated pharmacologically. Among the pharmacologically treated group, approximately half were prescribed glyburide (54.5%, N=5,873). In bivariate analysis, glyburide use was less common than insulin use in the Northeast (45.8% vs 54.2%) and more common in the South (56.4% vs 43.7%) and Midwest (54.9% vs 45.1%) regions of the US (Table 1). There was a small variation between regions in the proportion of women not treated pharmacologically, ranging from 88.1% to 93.8%. The proportion of women with comorbidities was generally similar between treatment groups, while those who were not treated pharmacologically had fewer co-morbid conditions (Table 2).

In multivariate analyses comparing glyburide with insulin, those in the Northeast and Midwest were less likely to be prescribed glyburide by 19% and 4%, respectively (PR 0.81 95%CI 0.76–0.87, p<0.0001; PR 0.96 95%CI 0.93–1.00, p<0.0001). Women with metabolic syndrome (PR 0.71, 95%CI: 0.50– 0.99), hyperandrogenism (PR 0.77, 95%CI: 0.62– 0.97), polycystic ovarian syndrome (PR 0.88, 95%CI: 0.78– 0.99), hypothyroidism (PR 0.89, 95%CI: 0.83– 0.96) or history of infertility treatment (PR 0.93, 95%CI: 0.86– 1.02) were less likely to be treated with glyburide (Table 3). Among women with an ICD-9 diagnosis code for obesity, there was no preference for one treatment over the other (PR 1.04, 95%CI: 0.98–1.10). Prior metformin use was not associated with initiation of glyburide (PR 1.01, 95%CI: 0.94– 1.09). The adjusted probability of being prescribed glyburide, varied by age with a 5% decrease for every 10 year increase in age (PR 0.95, 95%CI: 0.91– 0.99) (Figure 2). When compared to bivariate analysis, we did not observe important changes in the point estimates or confidence intervals after adjusting for covariates, except for obesity.

Among women initially treated with glyburide, 7.8% (N=461) received an additional medication or switched to a different drug class. The most common drug classes were insulin (N=387, 6.6%) or metformin (N=74, 1.3%). Among those initiating insulin, 1.1% (n=54) had a change in treatment prior to delivery. In this group, 0.8% (n=37) subsequently started glyburide and 0.3% (n=16) metformin. Women initiating glyburide were 8.1 times more likely to have a change in treatment before delivery (RR 8.1, 95%CI: 6.0–10.8).

DISCUSSION

We found a marked increase in the use of glyburide for the treatment of GDM in a commercially-insured United States cohort from 2000 to 2011 with a corresponding decrease in insulin use. This trend was coincident with the publication of results from randomized clinical trials (9–11) and observational studies (12–14, 20). Our results support findings from recent studies showing widespread use of glyburide despite lack of conclusive clinical evidence being available (3, 21). This trend need to be interpreted in the light of changes in GDM diagnosis and initiation of pharmacotherapy in this population over time.

Among the comorbidities of interest for which we had data, we did not find strong predictors of glyburide initiation. Women with infertility, polycystic ovarian syndrome and hyperandrogenism were more likely to be treated with insulin as were those with hypothyroidism or metabolic syndrome. Women with an obesity ICD-9-CM were equally

likely to be prescribed with glyburide or insulin. Because insulin resistance is increased in all these conditions, the degree of perceived insulin resistance could be an additional driver of initial choice of treatment for GDM.

Few studies have reported on changes in treatment (switching or augmenting) after initiation of medication. The majority focused on failure of glyburide (22–25). Less is known about failure after initiation on insulin therapy, where only one trial (Langer 2000, N=24/203) and one observational study (Gilson 2002, N=3/11) have reported frequencies between 12–27%. Although treatment failure could explain changes in treatment, tolerance or preference could also have a role. Our findings are consistent with previous literature where changes in treatment are more common in women initiating glyburide.

Little is known about the role of age on the preference to initiate treatment with oral agents among women with GDM. Our results provide evidence that age is one of the factors associated with choice of therapy. This was most evident in recent years after the dissemination of glyburide use (Figure 2). This may reflect more severe glucose intolerance in older women as there is some evidence that GDM severity increases with age. These findings are also consistent with studies showing that maternal age is a risk factor for failing to achieve glucose control with glyburide (23)

Due to the nature of healthcare claims data, we could not consider the influence of glucose tolerance test results, gestational age, biometrics (weight or height) or race-ethnicity on the choice of therapy. We believe our definition of GDM in combination with the exclusion of women who had early pharmacy claims for the drugs of interest yields a cohort of ‘true’ gestational diabetics. This approach was validated by Andrade et al who reported a positive predictive value of 85% (95%CI: 71–94%) (26). Also, we were limited to the ascertainment of obesity through the use of ICD-9-CM diagnosis codes. This was also validated by Andrade et al who reported a high positive predictive value (92%, 95%CI: 90– 94) but low sensitivity (33%) (26). While this suggests that there is considerable under-reporting of obesity, women with the code are likely obese. Though misclassification is likely not differential between the drug classes of interest, it could bias results towards the null and we therefore cannot rule out the possibility of an effect of obesity on choice of treatment. Because our population has employer-provided insurance, results from this study may not be generalizable to those covered by Medicaid or the uninsured. In a recent study by Albrecht et al, it was estimated that 61.4% of women with GDM would be privately insured. Therefore our results are reflective of patterns of care among a large, nationwide population(27).

Strengths of the study include sample size, ascertainment, and timing of medication use based on dispensed prescriptions. Our study likely includes women with different degrees of severity and is reflective of the full spectrum of patients treated in a variety of clinical settings. By restricting our cohort to women who were continuously enrolled in the year prior to delivery we assured that use of healthcare and pharmacy services would be observable throughout pregnancy. Therefore medication use in our study is based on pharmacy claims of dispensed drugs, which allowed us to identify the earliest prescription in

pregnancy. By using pharmacy claims, we likely have better ascertainment of initiation of treatment during pregnancy compared to self-report.

Dissemination of glyburide for the pharmacological treatment of GDM has been rapid and our findings indicate that since 2007 it has become the more common choice, particularly among younger, non-insulin resistant women. Due to its uptake, robust evaluation of glyburide's relative effectiveness is warranted to inform treatment decisions for women with gestational diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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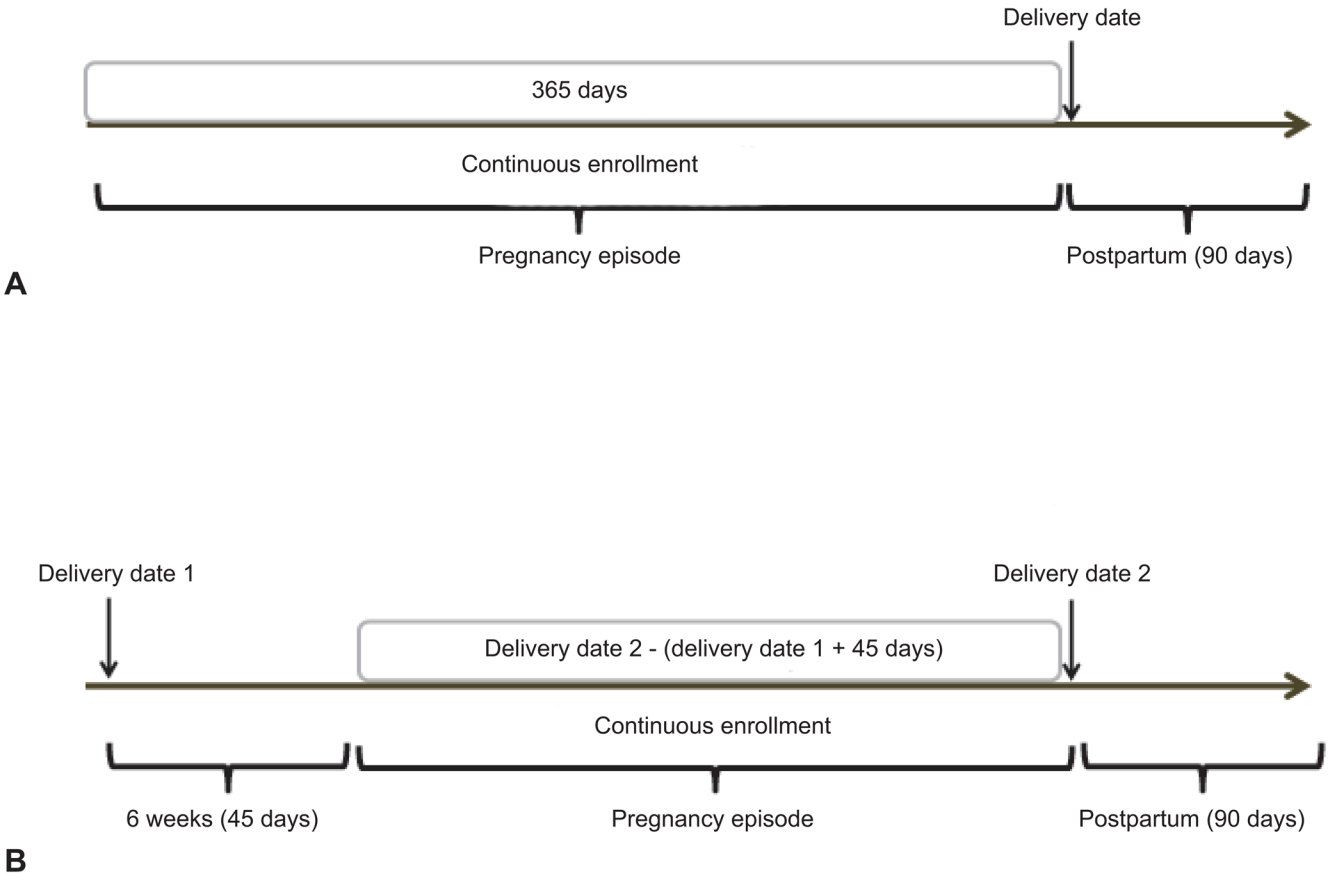

Figure 1. Identification of eligible pregnancies in cohort

After identifying date of earliest claim with a delivery code (Delivery Date) the pregnancy episode was defined as occurring 365 days before delivery (Fig 1*A*). For women with two pregnancies within a 12 month period, we identified the delivery dates for the first (Delivery Date 1) and second (Delivery Date 2) pregnancies. To avoid including diagnosis codes from the postpartum period of the first pregnancy, the pregnancy episode of the second pregnancy only started 45 days after Delivery Date 1 (Fig 1*B*).

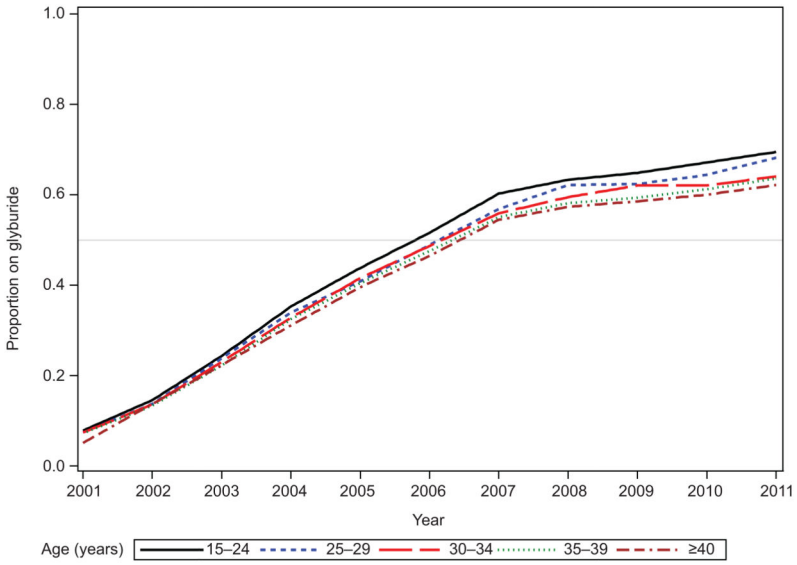

Figure 2. Trends in glyburide prescribing, by age group

Proportions were estimated from multivariable Binomial regression analyses, adjusted for all maternal comorbidities and prior metformin use. Reference line is threshold above which treatment with glyburide exceeded 50% (χ^2 test for linear trend for age p=0.02).

Table 1

Distribution of Women Treated With Glyburide (n=5,873) Among Women Treated With Glyburide or Insulin, by Calendar Year and Region

	Glyburide	Total
	%*	N=10,778
Calendar year		
2001	7.4	68
2002	13.5	155
2003	22.7	361
2004	33.1	631
2005	41.1	869
2006	48.4	881
2007	56.4	1,090
2008	59.4	1,278
2009	60.8	1,966
2010	62.3	1,807
2011	64.5	1,672
Region		
Northeast	45.8	1,305
Northcentral	54.9	2,965
South	56.3	4,283
West	55.3	2,152
Unknown	60.3	73

* Row percentages.

Table 2

Characteristics of Women Diagnosed With Gestational Diabetes Mellitus, Aged15–50 Years in a U.S.-Based Population, 2000–2011

	Insulin		Glyburide		Neither	
	n=4,905	**%**	**n=5,873**	**%**	**n=122,064**	**%**
Age, year- Mean(SD)	34 (4.7)		33 (4.7)		32 (5.2)	
Age, 5y categories						
15–19	4	0.1	3	0.06	1,665	1.4
20–24	99	2.4	124	2.5	7,278	6.0
25–29	730	17.4	940	18.9	30,352	24.9
30–34	1593	38	1860	37.3	45,053	36.9
35–39	1292	30.8	1508	30.2	29,396	24.1
40–44	442	10.5	523	10.5	7,748	6.3
>=45	34	0.8	28	0.6	572	0.5
Comorbidities						
Infertility treatment	283	6.7	280	5.6	3,998	3.3
Hypothyroidism	349	8.3	353	7.1	6,908	5.7
PCOS	171	4.1	162	3.2	2,597	2.1
Hyperprolactinemia	14	0.3	11	0.2	257	0.2
Hyperandrogenism	67	1.6	99	2.0	2,776	2.3
Metabolic syndrome	30	0.7	20	0.4	343	0.3
Obesity	305	7.3	499	10.0	5,624	4.6
No comorbidities	3154	75.2	3773	75.7	102,069	83.6
Metformin use						
Use in early pregnancy	283	6.7	317	6.4	2,551	2.1

Neither: women without pharmacologic treatment for GDM within 150 days of delivery. Metformin use: Prescription claim for metformin in early pregnancy (>150 days before delivery).

SD, standard deviation; PCOS, polycystic ovary syndrome.

Table 3

Association of Calendar Year and Maternal Characteristics With Initiation of Glyburide Compared With Insulin

	Crude		Adjusted*	
	PR	**95%CI**	**PR**	**95%CI**
Calendar year				
2001	0.13	0.06 – 0.30	0.13	0.06 – 0.30
2002	0.23	0.15 – 0.35	0.23	0.15 – 0.34
2003	0.36	0.29 – 0.44	0.35	0.29 – 0.44
2004	0.53	0.47 – 0.60	0.52	0.46 – 0.59
2005	0.63	0.57 – 0.69	0.63	0.57 – 0.69
2006	0.74	0.68 – 0.81	0.74	0.68 – 0.80
2007	0.88	0.83 – 0.95	0.88	0.82– 0.94
2008	0.93	0.88 – 0.99	0.93	0.88 – 0.99
2009	0.94	0.89 – 0.99	0.93	0.88 – 0.99
2010	0.97	0.91 – 1.02	0.96	0.91 – 1.00
2011†	1.00		1.00	
Age 10y				
Change(Continuous)	0.96	0.93 – 1.00	0.95	0.91 – 0.99
Comorbidities				
Infertility treatment	0.91	0.84 – 0.99	0.93	0.86 – 1.02
Hypothyroidism	0.92	0.85 – 0.99	0.89	0.83 – 0.96
PCOS	0.90	0.80 – 1.00	0.88	0.78 – 0.99
Hyperandrogenism	0.80	0.64 – 1.00	0.77	0.62 – 0.97
Metabolic syndrome	0.74	0.52 – 1.03	0.71	0.50 – 0.99
Obesity	1.16	1.09 – 1.23	1.04	0.98 – 1.10
Metformin use				
Any use prior to index date	1.00	0.92 – 1.07	1.01	0.94 – 1.09

*All prevalence ratio estimates were adjusted for all other variables in the table.

†Reference category

PR prevalence ratio; CI, confidence interval; PCOS, polycystic ovary syndrome.